Preventing prematurity in twins

Twin pregnancies still carry a higher risk than single pregnancies: in recent series\(^1\)–\(^5\) the perinatal mortality has been between 8% and 12%. Some complications, such as pre-eclampsia and anaemia, are seen more frequently in twin pregnancies,\(^3\)\(^,\)\(^5\) but the single most important cause of fetal wastage is prematurity.\(^6\)\(^,\)\(^7\) Some 20–30\(^\circ\)\(^\circ\), of twin pregnancies end before the 37th week\(^2\)\(^,\)\(^3\)\(^,\)\(^5\)\(^,\)\(^8\) with the associated risk of the infants succumbing to the respiratory distress syndrome.\(^8\)

Why premature labour should be so common is not fully understood: overdistension of the uterus is probably not the only factor,\(^7\) and a diminution in uterine blood flow may also be relevant.\(^9\)

In an attempt to prevent premature labour some maternity units advise admission to hospital during the “danger period” between the 30th and 37th weeks. Some obstetricians recommend bed rest for all women carrying twins\(^1\) and some only for primigravidae,\(^7\)\(^,\)\(^8\) among whom the risk of premature delivery is higher.\(^2\) Yet there is no clear proof that bed rest is effective in preventing premature delivery. Some investigators have found a significant prolongation of pregnancies,\(^4\) while others have reported that bed rest has no effect on the incidence of prematurity.\(^2\)\(^,\)\(^10\) Furthermore, twins who do remain in utero are at risk from placental insufficiency.\(^2\)\(^,\)\(^6\)

Bed rest may benefit these fetuses by promoting intrauterine growth,\(^4\)\(^,\)\(^10\) but if that is so then bed rest should logically be continued beyond the 37th week.\(^4\) At present the benefits of bed rest in promoting fetal growth have been shown only by retrospective surveys,\(^3\)\(^,\)\(^10\) and these may be criticised on the grounds that patients who refused treatment may have been the very ones at highest risk.\(^9\)

A recent study in Liverpool\(^1\) has compared the results in uncomplicated twin pregnancies treated in three units of the same hospital. One unit used no prophylactic treatment; one advised bed rest for all twin pregnancies; and the third routinely inserted a cervical suture as soon as twin pregnancy was diagnosed—a method of treatment recommended on theoretical grounds\(^3\)\(^,\)\(^9\) but unproved by clinical trials. The three groups of patients did equally well: neither form of treatment prolonged the pregnancies or increased the weights of the babies in comparison with the untreated group. Pointing out that bed rest disrupts family life and carries a risk of thromboembolism, the Liverpool group concluded that neither treatment is justified for a woman with an uncomplicated twin pregnancy.

At present, therefore, there seems to be no effective prophylaxis that can be offered to women expecting twins, nor are the prospects particularly bright. Beta-sympathomimetic agents such as ritodrine and isoxsuprine are successful in stopping established premature labour in around 80\(^\circ\)\(^\circ\), of cases, being given at first intravenously and then orally.\(^11\)

It has been suggested that they might be used in twin pregnancies,\(^7\) but clearly if beta-sympathomimetic drugs were given as a routine they could be administered only in the less effective oral form. One double-blind trial\(^12\) suggested that oral ritodrine is ineffective as a prophylaxis against premature labour, but no similar study of twin pregnancies has yet been reported. The beta-sympathomimetics have important side effects on the cardiovascular system\(^11\) and should not be used routinely until there is clear evidence of their effectiveness.

Indeed, we may have no reliable means of preventing premature labour until we understand its pathogenesis better. Meanwhile the obstetrician can do little more than ensure that twins are diagnosed early in pregnancy, since late diagnosis is associated with a greatly increased mortality.\(^13\) While routine bed rest may be unjustified for all cases, selective admission of high-risk patients is still wise.\(^2\) If premature labour begins in hospital it can be treated by the usual methods,\(^11\)\(^,\)\(^14\) though their effectiveness in twin pregnancy has not been proved.

Control of penicillinase-producing gonococci

Gonococci with decreased sensitivity to penicillin have become increasingly common throughout the world. These strains, in which the minimum inhibitory concentration (MIC) of penicillin ranges up to 1–2 \(\mu g\) \(\text{ml}^{-1}\), often also show decreased sensitivity to other antibiotics such as tetracycline, streptomycin, and erythromycin. The genetic determinants of this type of resistance are chromosomal, and it can be produced in vitro by transformation of piloted strains by DNA. Resistant strains also show decreased permeability of the cell envelope and decreased binding of penicillin to the cell membrane, compared with sensitive strains.\(^1\)
The sudden appearance last year of strains of gonococci which have acquired the ability to produce a \( \beta \)-lactamase (penicillinase) and so become completely resistant to penicillin and ampicillin has serious implications for the control of gonorrhoea. These strains were first seen in the United States, mainly in servicemen returning from the Far East, and in an apparently unconnected outbreak of infections on Merseyside.\(^1\)

They have since been identified in at least 11 countries.\(^1\)

Both Roberts and Falkow\(^1\) and Eisenstein et al\(^3\) have shown that this new type of resistance is mediated by plasmids—extrachromosomal loops of DNA. Almost all gonococci contain a plasmid of molecular weight 2.5 \( \times \) 10\(^6\), and some a larger one of 24.5 \( \times \) 10\(^6\). Strains from the USA and Far East producing \( \beta \)-lactamase contain an additional plasmid of molecular weight 4.4 \( \times \) 10\(^6\) and similar strains from the Liverpool outbreak one of molecular weight 3.2 \( \times \) 10\(^6\); both of these carry the genetic information coding for \( \beta \)-lactamase production. The difference in molecular weight of these two R plasmids suggests that the USA Far East and Liverpool strains have originated separately.\(^1\)

The Far Eastern strains producing \( \beta \)-lactamase differ among themselves in their nutritional requirements and chromosomal antibiotic resistance genes; this suggests that in this area there has been a considerable dissemination of the R plasmid among different strains of gonococci rather than the spread of a single resistant strain in the population.

Transformation has not proved possible in vitro of sensitive gonococci to \( \beta \)-lactamase production by DNA from \( \beta \)-lactamase producers. Transfer seems to be due to conjugation between gonococci, and probably only those strains having the large 24.5 \( \times \) 10\(^6\) plasmid can act as donors. Hence this plasmid may have a sex factor activity and transfer of the smaller resistance plasmid is promoted during conjugation. Other findings suggest that this large plasmid may promote transfer of chromosomal genes; if that is confirmed the emergence of multiply resistant penicillinase-producing strains will be a possibility. The large sex factor plasmid was found in three of the nine Far Eastern strains but in none of the three Liverpool strains studied. In mating experiments Eisenstein and his colleagues\(^6\) were able to transfer the ability to produce \( \beta \)-lactamase from gonococci to Escherichia coli and Neisseria flava. This has serious implications; the possibility of transfer in vivo to meningococci is especially worrying.

Where did the first \( \beta \)-lactamase producing gonococcus get its R plasmid from and why has it taken so long to do so? Percival et al\(^7\) found that the substrate profile of the Liverpool strains was similar to that of an E coli TEM \( \beta \)-lactamase, and in isoelectric focusing experiments both enzymes gave a band focusing at pH 5.4. Rectal lesions are common in women with gonorrhoea, and E coli and gonococci must have coexisted in this site on innumerable occasions. Haemophilus influenzae may also have been responsible for this unwelcome gift. Plasmid-mediated \( \beta \)-lactamase producing strains of haemophilus have emerged during the past few years. Pathogenic gonorrhoea transmitted by orogenital sexual practices provides ample opportunity for these two organisms to meet.

The potential threat which penicillinase-producing gonococci pose to the control of gonorrhoea is obvious, but it should be kept in perspective. In Britain the outbreak on Merseyside seems to have been contained: only a handful of strains have been seen in other parts of the country, most of which originated from infections in the Liverpool area. This is a tribute to the efficiency of the contact tracing methods used there, and these form the major method for containment. Screening gonococcal isolates for sensitivity to penicillin by a simple disc method will rapidly identify strains needing further investigation; full sensitivity studies are also essential in all patients failing to respond to penicillin. Spectinomycin or cefuroxime are effective for treating patients known to be infected with \( \beta \)-lactamase producing gonococci or their contacts.

If the prevalence of \( \beta \)-lactamase producing strains in Britain remains as low as it is now there is no need to abandon the use of penicillin or ampicillin. In high prevalence areas, such as the Philippines—where 20-40\(^\circ\), of prostitutes are said to carry these strains—a reappraisal of treatment methods is clearly needed. But with the global distribution of these strains and the speed of air travel inevitably further resistant strains will be imported into Britain. We need to identify and eradicate them before they can establish themselves in the community.

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### Polyamines as markers of response to chemotherapy of cancer

The polyamines putrescine, spermidine, and spermine are small cations now thought by some researchers to be vital as regulators of tissue growth. This seems a long way from earlier ideas in which putrescine was considered a product of bacterial decay of mammalian tissue and spermidine and spermine were thought simply to be degradation products excreted into seminal fluid. In fact polyamines and their biosynthetic enzymes are ubiquitous.\(^1\) The increase of RNA in cells as they grow and reproduce is paralleled by an increase of spermidine and preceded by a build up of putrescine. In mammalian tissues it is the decarboxylation of ornithine that is the source of putrescine, which in turn yields spermidine and spermine. The enzyme ornithine decarboxylase has an unusually high turnover rate in mammalian cells; its level is normally quite low but rises rapidly in response to growth stimuli.

At this point the story passes on to weaker ground. While it can be shown that polyamines have an affinity for nucleic acids and can stimulate protein synthesis both in vivo and in vitro, no specific mechanism has been firmly established for the action of polyamines in vivo; and many biochemists are trying to determine the part that these simple molecules play in controlling nucleic acids and the synthesis of proteins. At present it seems that if they are concerned in the regulation of tissue growth then they behave in a different fashion from other forms of well-established growth regulators, for their concentrations in cells are far too high according to current biochemical theory of the action of regulators. Furthermore, though the activities of ornithine decarboxylase can change quickly, such a mechanism is still comparatively slow in terms of the speed of biochemical reactions.

Diane Russell has argued strongly that these compounds deserve more attention as biochemical markers of cancer and has recently reviewed the evidence. Techniques for isolating...